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PATENT
Attorney Docket No.: DALHO1290-1
(028614-1102)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Sawynok et al.

Application No.: 09/700,625

Filing Date: February 1, 2001

For: USE OF TRICYCLIC ANTIDEPRESSANTS FOR LOCAL ANALGESIA

Group Art Unit: 1615

Examiner: T. Ware

CERTIFICATION
I hereby certify that the documents referred to as enclosed herein are being sent via Federal Express for next business day delivery to: Commissioner for Patents, Washington, D.C. 20231, Attn: Examiner Todd D. Ware, 7th Floor Reception, 1911 S. Clark Place, Crystal Mall 1, Arlington, VA 22202

Stephen E. Reiter
Name of person mailing paper

Signature August 20, 2002
Date

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Commissioner for Patents
Washington, D.C. 20231
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SUPPLEMENTAL DECLARATION UNDER 37 C.F.R. § 1.131

Sir:

We, Jana Sawynok, Mike Esser and Allison Reid, being duly warned, hereby individually and collectively declare and say that:

1. We are the joint co-inventors of the invention disclosed and claimed in the above-referenced application.

2. We understand that October 28, 1997 is the effective prior art date of a reference cited by the Examiner, U.S. Patent No. 5,922, 341 to Smith and Place.

3. The present invention was completed prior to October 28, 1997 during experiments performed at Dalhousie University, Halifax, Nova Scotia, Canada.

4. We understand that the Examiner has asserted that our previously submitted declaration (mailed with the response of February 11, 2002) allegedly does not provide support for second or third generation antidepressants.

5. The conception of the present invention is indeed demonstrated by the evidence provided in our previously submitted declaration because the choice of amitriptyline as a prototype antidepressant was made based on one of its recognized functions as a modulator of adenosine, and not based on its pharmaceutical classification as a particular type of antidepressant.

6. Specifically, prior work conducted in the laboratory of Dr. Jana Sawynok had demonstrated that peripheral modulation of the pain signal could be achieved by altering levels of adenosine using an adenosine kinase inhibitor. This pain modulating effect based on altering levels of adenosine was further augmented with an adenosine deaminase inhibitor. This study demonstrated that endogenous adenosine, which accumulates following peripheral inhibition of adenosine kinase, mediates pain via activation of an adenosine receptor. See Sawynok *et al.*, *Pain* **74**:75-81 (1998); submitted for publication May 13, 1997; Exhibit A.

7. At this point, we conceived that a variety of compounds that exhibit an ability to modulate adenosine levels, in effect, comparable to the previously studied adenosine kinase inhibitor and/or adenosine deaminase inhibitor, could also be used in effective compositions for locally modulating pain.

8. For example, it has long been known in the art that adenosine pathways in the central nervous systems were implicated in the mode of action of several centrally active drugs including antidepressants. See, *e.g.*, Williams, *Prog. Neuropsychopharmacol. Biol. Psychiatry* **7**:443-450 (1983); Abstract provided in Exhibit B. Indeed, a variety of classes of antidepressants, including both tricyclic and non-tricyclic antidepressants, have long been known to have effects on adenosine uptake. See, *e.g.*, Phillis and Wu, *Comp. Biochem. Physiol.* **72C**:179-187 (1982); Exhibit C. Moreover, a specific example of a second generation or third generation antidepressant contemplated in our specification, trazodone, has also been shown to

be an inhibitor of adenosine deaminase in particular. See, *e.g.*, Sheid, *Res. Commun. Chem. Pathol. Pharmacol.* **47**:149-152 (1985); Abstract provided in Exhibit D.

9. Thus, we conceived of the present invention based on the recognition that any antidepressant having an ability to modulate adenosine levels as one of its biological effects, could be used in methods for producing local analgesia and incorporated into compositions as claimed in the present application.

10. The experiments summarized in our previously submitted declaration using amitriptyline provide proof that an exemplary antidepressant could be used in methods for producing local analgesia and incorporated into compositions as claimed. Therefore, these experiments provide demonstrative evidence that we had the requisite means to produce the claimed compositions for local administration comprising any antidepressant and a vehicle suitable for topical administration.

11. Additional experiments were diligently performed following these preliminary studies over a period of less than 7 months, which are reflected in the specification as filed in the original priority application, USSN 09/081,709, filed on May 19, 1998 (now issued as U.S. Patent No. 6,211,171). Exhibit E.

12. We each individually further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

Aug 1/2002
Date

Jana Sawynok
Jana Sawynok

Aug 4/02
Date

Mike Esser
Mike Esser

Aug 1/02
Date

Allison Reid
Allison Reid